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Title: Interaction between prenatal risk and infant parasympathetic and sympathetic stress reactivity predicts early aggression

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Abstract

Nonreciprocal action of the parasympathetic (PNS) and sympathetic (SNS) nervous systems, increases susceptibility to emotional and behavioral problems in children exposed to adversity. Little is known about the PNS and SNS in interaction with early adversity during infancy. Yet this is when the physiological systems involved in emotion regulation are emerging and presumably most responsive to environmental influences. We examined whether parasympathetic respiratory sinus arrhythmia (RSA) and sympathetic pre-ejection period (PEP) response and recovery at six months, moderate the association between cumulative prenatal risk and physical aggression at 20 months ($N=113$). Prenatal risk predicted physical aggression, but only in infants exhibiting coactivation of PNS and SNS (i.e., increase in RSA and decrease in PEP) in response to stress. These findings indicate that coactivation of the PNS and SNS in combination with prenatal risk is a biological marker for the development of aggression.

Keywords: Aggression, stress reactivity, autonomic nervous system, prenatal risk, infancy

Running head: Infant stress reactivity, prenatal risk and aggression

Exposure to adversity during the prenatal period, such as maternal psychiatric problems, substance (ab)use, single parenthood and poverty, has been shown to predict aggression in childhood that persists into adolescence and adulthood (Côté, Vaillancourt, LeBlanc, Nagin, & Tremblay, 2006; Hay et al., 2011; NICHD Early Child Care Research Network, 2004). Yet, not all children seem to be equally affected by adversity. Guided by theories of differential susceptibility (Belsky & Pluess, 2009) and biological sensitivity to context (Boyce & Ellis, 2005), a number of studies have demonstrated that individual differences in stress reactivity, as measured by indices of the cardiac autonomic nervous system (ANS), can predispose or protect against the effects of adversity on children's behavioral maladjustment (e.g. El-Sheikh & Erath, 2011). Although these studies provide important insights into physiological measures of susceptibility, they have focused mostly on older children. Little is known about the role of the cardiac ANS in interaction with early adversity during infancy when the physiological systems involved in emotion regulation are emerging and presumably most responsive to environmental influences (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008; Laurent, Harold, Leve, Shelton, & Van Goozen, 2016).

Altered ANS functioning has been consistently linked to aggression in children, adolescents and adults (Van Goozen, Fairchild, Snoek & Harold, 2008). The ANS is comprised of a sympathetic (SNS) and parasympathetic (PNS) branch. PNS activity is often assessed by respiratory sinus arrhythmia (RSA). RSA is the heart rate variability at the frequency of respiration (Cacioppo, Uchino, & Berntson, 1994), and is considered to index the neural control of the heart via the vagus nerve (Porges, 2007). During restful periods, the vagus exerts an inhibitory influence on the heart acting as a 'brake' by increasing vagal output to the sino-atrial (SA) node of the heart and limiting sympathetic influences which contribute to a slow and steady heart rate. In response to stress, the vagal 'brake' is disengaged resulting in a decrease in vagal output to the SA node of the heart and thus contributing to an increase

in heart rate (Porges, 2007). If withdrawal of the vagal ‘brake’ is not sufficient to manage a stressor, the sympathetic activity is expected to increase in order to prepare the body for a more active stress response.

The majority of research examining stress reactivity in young children has focused on RSA or global measures of cardiac autonomic functioning like HR without specific assessments of activity within the sympathetic branch. Pre-ejection period (PEP) reflects the time interval between the onset of the heartbeat and ejection of blood into the aorta (Cacioppo et al., 1994) and is commonly used as an index of myocardial contractility and sympathetic control of the heart (Berntson et al., 1994). Both RSA and PEP are used as indicators of the complex processes that underlie responsiveness of the ANS to a changing environment, e.g., from rest (baseline) to challenge or vice versa.

Low baseline PNS activity, as indicated by RSA, has been identified as a vulnerability factor that exacerbates the relation between adversity (e.g. marital conflict, parental drinking problems) and children’s externalizing behavior (El-Sheikh, 2005a; El-Sheikh, Harger, & Whitson, 2001). Other studies have measured RSA reactivity to stress, with decreases in RSA in response to stress considered to be indicative of better adaptation (El-Sheikh & Erath, 2011). RSA withdrawal in response to stress has been associated with lower levels of externalizing behavior in the context of adversity (El-Sheikh, 2001; Katz, 2007), although findings have been inconsistent (Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010). Studies investigating interactions between adversity and SNS activity (measured as skin conductance level [SCL] in most studies) indicate that either very low or very high baseline levels of SCL and high SCL reactivity may increase the risk of aggression and externalizing behavior in the context of adversity (El-Sheikh, 2005b; El-Sheikh, Keller, & Erath, 2007).

It is clear that ANS functioning has important implications for the association between adversity and the development of aggression. However, such associations may be less

straightforward in infancy. For example, recent studies indicated a stronger positive relation between higher (rather than lower) baseline RSA and (externalizing) problem behavior in infants and toddlers exposed to a more negative caregiving environment (Conradt, Measelle, & Ablow, 2013; Eisenberg et al., 2012). Measures of RSA reactivity and SNS functioning in infants have not been studied as moderators of relations between early adversity and aggression before, although there is one study in toddlers reporting no effects of RSA reactivity (Eisenberg et al., 2012).

Adaptation to stressful contexts requires a delicate balance in the operation of both the PNS and SNS (Porges, 2007), and the synergistic action of both systems determines the effectiveness of regulation (Berntson, Cacioppo, & Quigley, 1991). Although the effects of both branches of the ANS on the heart is generally believed to be reciprocal, with increased activity in one branch and decreased activity in the other, reactivity in both branches can also be nonreciprocal (i.e., increased or decreased activity of both branches at the same time; Berntson et al., 1991). Reciprocal cardiac PNS activation, with increased PNS stimulation and decreased SNS stimulation on the heart, is expected during calm states, while reciprocal SNS activation (i.e., increased SNS activity and decreased PNS activity) is more adaptive when confronted with challenging stressful situations. Previous studies have suggested that reciprocal cardiac SNS activation in response to stress is normative in children, adolescents and adults (Alkon, Boyce, Davis, & Eskenazi, 2011; Berntson et al., 1991; Salomon, Matthews, & Allen, 2000), and linked to better emotion regulation in young children (Stifter, Dollar, & Cipriano, 2011). Conversely, nonreciprocal activation of PNS and SNS, as indicated by coactivation (i.e., increased activity in both the PNS and SNS) and coinhibition (i.e., decreased activity in both the PNS and SNS), has been linked to more externalizing problems in school-aged children in the context of marital conflict, compared to patterns of reciprocal SNS activation or reciprocal PNS activation (El-Sheikh et al., 2009). Similar

findings have been reported in the context of maltreatment predicting aggression in girls (Gordis, Feres, Olezeski, Rabkin, & Trickett, 2010).

So far, there have been no studies that we know of that have examined measures of both PNS and SNS functioning in infancy as potential moderators of the effects of early adversity on outcome in toddlerhood. Elucidating how early physiological systems increase or decrease susceptibility to aggression, may enhance our ability to identify children at risk of aggression at an early age, before developmental trajectories begin to be set.

In the present study, we investigated the interaction between ANS response to and recovery from stress measured in 6-month-old infants, taking into consideration both the PNS and SNS, and prenatal risk in predicting physical aggression at 20 months of age. We were specifically interested in cumulative risk as previous work has shown a dose-dependent relation between the presence of multiple risk factors and child adjustment, with increases in the number of risk factors being associated with increased levels of problems (Appleyard, Egeland, van Dulmen, & Sroufe, 2005). We measured parasympathetic RSA and sympathetic PEP response and recovery from stress. Although previous studies involving PNS and SNS interactions have focused on SCL (El-Sheikh et al., 2009; Gordis et al., 2010), PEP is considered to be a more direct measure of cardiac SNS activity (Cacioppo et al., 1994), that can be reliably measured in infants (Alkon et al., 2006; Quigley & Stifter, 2006). We hypothesized that higher levels of *coactivation* and *coinhibition* would exacerbate the relation between cumulative prenatal risk and physical aggression, whereas, *reciprocal PNS activation* and *reciprocal SNS activation* would attenuate the association between cumulative risk and physical aggression.

Methods and Materials

Participants

The participants in this study were part of an ongoing longitudinal study into neurobiological and neurocognitive predictors of early behavior problems (Mother- Infant NeuroDevelopment Study in Leiden, The Netherlands [MINDS – Leiden]). We oversampled women based on the presence of one or more risk factors (see criteria under Cumulative risk). The sample was composed of 113 mothers and their infants (55.8% males) who had completed the prenatal home-visit during the third trimester of pregnancy (T1), and the postpartum home-visits at six (T2) and 20 months (T3). The mean age of the children was 6.03 months ($SD=.41$, range 5-7 months) at T2 and 19.94 months ($SD=.81$, range 18-24 months) at T3. The mothers were on average 22.96 years ($SD=2.12$, range 17-27 years) at T1. Approximately 96% of the mothers had a partner (87.6 % was married or living with a partner) and 32.7% of the mothers had a high educational level (Bachelor's or Master's degree). Families were predominantly Caucasian (88.5%).

Of the 136 mothers originally enrolled in the study at T1, 10 did not participate at T2, and another 13 dropped out between T2 and T3. Main reasons for families dropping out were inability to contact, moving away or too busy. Sample attrition was unrelated to demographic variables (i.e., maternal age, ethnicity, marital status, educational level; $ps>.05$). However, mothers who dropped out were more often single ($\chi^2(1) = 8.41, p=.013$).

The study was approved by the ethics committee of the Department of Education and Child Studies at the Faculty of Social and Behavioral Sciences, Leiden University, and by the Medical Research Ethics Committee at Leiden University Medical Centre. Informed consent was obtained from all parents of infants included in the study. Mothers were compensated for

each completed home or laboratory visit and children were given a small present for their participation.

Procedures

The protocol during the six-month home-visit (2hrs), included attachment of cardiac monitoring equipment to the infant's chest and back after which they watched a 2-minute relaxing movie while lying on a blanket, followed by two procedures designed to elicit physiological responses to social stress (Still Face Paradigm) and frustration (Car seat). The social stress and frustration tasks were administered with a break in between to limit carry over effects. Infants were only assessed in the next procedure when they were calm and displayed no distress. The home-visits were scheduled at a time of the day when mothers deemed their infant to be most alert.

The Still Face Paradigm (SFP; Mesman, Van IJzendoorn, & Bakermans-Kranenburg, 2009) is a well-established social stress paradigm comprising a sequence of three 2-minute episodes during which the mother is asked to interact normally with the infant (SFP baseline), then withhold interaction (SFP social stress), and then resume interaction (SFP recovery) (for a more detailed description of the SFP, see Suurland, Van der Heijden, Smaling, Huijbregts, Van Goozen, & Swaab, 2016). The Car Seat (CS) task, adapted from the Laboratory Temperament Assessment Battery Pre-locomotor version (Lab-TAB; Goldsmith & Rothbart, 1999), was used to measure infant physiological response to a frustrating event. Following a 2-minute baseline (CS baseline), mothers placed their infants in a car seat and stood 1 meter away from their child. After 1 minute of restraint (CS frustration), a 2-minute recovery period (CS recovery) followed in which mothers were allowed to hold their child and interact as they normally would. Mothers were instructed to remain neutral and refrain from comforting or speaking to the child during the CS frustration episode.

During the challenge episodes, infant distress (i.e., whining, fussing or crying) was coded by trained raters from videotaped recordings according to scales of the Mother Infant Coding System (Miller, McDonough, Rosenblum, & Sameroff, 2002) for the SFP; the Lab-TAB coding system (Goldsmith & Rothbart, 1999) was used for the CS. During the SFP social stress and the CS frustration episodes respectively 26.8% and 25.5% of the infants showed signs of distress.

Measures

Physiological measures. Parasympathetic RSA and sympathetic PEP were monitored continuously with the Vrije Universiteit Ambulatory Monitoring System (VU-AMS 5fs; De Geus, Willemsen, Klaver, & Van Doornen, 1995; Willemsen, De Geus, Klaver, Van Doornen, & Carroll, 1996). The VU-AMS device continuously recorded electrocardiogram (ECG), and impedance cardiogram (ICG) measures; basal thorax impedance (Z_0), changes in impedance (dZ), and the first derivative of pulsatile changes in transthoracic impedance (dZ/dt). The ECG and dZ/dt signal were sampled at 1000 Hz, and the Z_0 signal was sampled at 10Hz. The VUDAMS software suite version 2.0 was used to extract mean values of heart rate (HR), RSA, and PEP across SFP baseline (2 minutes), SFP social stress (2 minutes), and SFP recovery (2 minutes), and CS baseline (2 minutes), CS frustration (1 minute), and CS recovery (2 minutes).

R-peaks in the ECG, scored by the software, were visually checked and adjusted manually when necessary. RSA was derived by the peak-trough method (De Geus et al., 1995; Grossman, Van Beek, & Wientjes, 1990), which combined the respiration (obtained from filtered [0.1 – 0.4 Hz] thoracic impedance signal) and inter beat interval (IBI) time series to calculate the shortest IBI during heart rate acceleration in the inspiration phase and the longest IBI during deceleration in the expiration phase (De Geus et al., 1995). RSA was

defined as the difference between the longest IBI's during expiration and shortest IBI's during inspiration. Automatic scoring of RSA was checked by visual inspection of the respiratory signal from the entire recording. RSA was not calculated if >30% of the data in an episode were missing.

PEP is the time interval between the onset of the ventricular depolarization (Q-wave onset) and the onset of left ventricular ejection of blood into the aorta (B-point on the Dz/dt complex (De Geus et al., 1995). Average dZ/dt waveforms were derived by the software. PEP was automatically scored from the Q-wave onset (opening of the aortic valve) on the ECG and the B-point on the dZ/dt waveform. Each automated scoring was checked and corrected manually when necessary (Riese et al., 2003). In case waveforms were morphologically distorted in such a way that visual correction of automated scoring was not possible, these waveforms were discarded. The procedure of interactive visual scoring was done independently by two trained raters. Post-scoring, the raters chose a consensus for the points where their judgment did not overlap, and these were retained for analysis; inter-rater reliability (intraclass correlation, ICC) was .949.

Cumulative risk. During the third trimester of pregnancy (between 26 and 40 weeks gestation, $M = 29.78$, $SD = 3.63$), mothers were screened for the presence of risk factors (see for a more elaborate description of these criteria: Smaling et al., 2015; Suurland et al., 2016), including current psychiatric disorder(s) with the Dutch version of the Mini- International Neuropsychiatric Interview (MINI-plus; Van Vliet, Leroy, & Van Megen, 2000), substance use (alcohol, tobacco and/or drugs) during pregnancy, no secondary education, unemployment, self-reported financial problems, limited or instable social support network, single status, and maternal age <20 years. The cumulative risk score was computed as the sum of risk factors present (maximum number of risk factors was 10), with $M=.67$, $SD=.93$ (range 0-3). There were 66 mothers with no risk factors, 25 with one risk factor, 15 with two risk

factors, and 7 with three risk factors. The prevalence of the different risk factors among mothers with one or more risk factors (41.6%) was: 55.3% current psychiatric diagnosis, 4.3% alcohol, 44.7% smoking, 2.1% drugs, 10.6% single status, 10.6% unemployed, 4.3% no secondary education, 8.5 % financial problems, 8.5% limited social support, 14.9% age <20 years.

Maternal reports of physical aggression. Mothers reported on their child's physical aggression at 20 months using the 11-item Physical Aggression Scale for Early Childhood (PASEC; Alink et al., 2006). Mothers indicated whether their child had shown physically aggressive behaviors (e.g. 'hits', 'kicks', 'destroying things') in the past two months on a 3-point Likert scale (0 = 'not true to 2 = 'very true or often true'). A total score for physical aggression was calculated by summing item scores (range 0-22). Internal consistency (Cronbach's alpha) was .73.

Missing data

Approximately 12% of ANS data were missing across the SFP and CS episodes. Missing data were due to dyads that did not complete the SFP or CS because the infant became too fussy (3.8%), loose electrodes (5.7%), equipment failure (1.9%), or excessive child movement in which case PEP and/or RSA could not be scored (88.6%). Missing data were not systematically related to demographic and obstetric variables (see variables listed in Table 1; $ps > .250$) or cumulative risk and physical aggression ($ps > .250$). Main analyses were conducted based on the number of infants for which there was data (see Supplementary Table 1 for available ANS data across SFP and CS episodes).

Data analysis

All variables were examined for outliers and violations of specific assumptions applying to the statistical tests used. Variables with values that exceeded $>3SD$ from the group mean were recoded to the next extreme value within $3SD$ from the mean (across all SFP and CS episodes there were 14 outliers for RSA and two outliers for PEP). Because RSA was skewed at baseline, the emotional challenge tasks, and recovery, its natural logarithm (lnRSA) was used in the analyses.

Baseline levels of lnRSA and PEP were significantly correlated with lnRSA and PEP challenge scores ($rs=.27$ to $.84$, $ps<.001$). Further, lnRSA and PEP challenge scores were significantly correlated with lnRSA and PEP recovery scores ($rs=.53$ to $.87$, $ps<.001$). To control for initial levels of arousal, response and recovery variables for lnRSA and PEP were computed as standardized residualized change scores (Eisenberg et al., 2012; El-Sheikh et al., 2009). The standardized residualized change scores for response to challenge were obtained by regressing the challenge scores on the baseline levels and for recovery from challenge by regressing the recovery scores on the challenge scores. This was done separately for the SFP and the CS. The standardized residualized change scores for lnRSA and PEP during response and recovery on the SFP were significantly correlated with the standardized residualized change scores for lnRSA and PEP during response and recovery on the CS ($rs=.24$ to $.28$, with $ps=.021$ to $.009$). Therefore, the residualized change scores of lnRSA and PEP on the SFP and CS were averaged to create four indices: lnRSA response and PEP response (average SFP and CS) and lnRSA recovery and PEP recovery (average SFP and CS). Negative values reflect lnRSA and PEP decreases (i.e., greater PNS suppression and greater SNS activation respectively), while positive values reflect lnRSA and PEP increases (i.e., greater PNS activation and greater SNS suppression respectively).

Preliminary analyses tested for potential covariates (demographic and obstetric characteristics). Hierarchical linear regression analyses were conducted to examine the

interactive effects of cumulative risk and ANS response and recovery on physical aggression. Two sets of regression analyses were conducted: (1) lnRSA and PEP response measures, and (2) lnRSA and PEP recovery measures. All variables were centered to their mean prior to analyses (Aiken & West, 1991). Step 1 included cumulative risk, Step 2 included lnRSA and PEP, Step 3 included all two-way interactions between cumulative risk, lnRSA and PEP, and Step 4 included the three-way interaction between cumulative risk, lnRSA, and PEP. Significant interaction effects were examined following procedures recommended by Aiken and West (Aiken & West, 1991) by plotting regression lines of the relation between cumulative risk and physical aggression at 0 risk factors and 1.6 risk factors (i.e., mean number of risk factors for the group of infants with ≥ 1 risk factors) and 1 *SD* above and below the mean for the moderators (lnRSA response/lnRSA recovery, and PEP response/PEP recovery).

The scores for the cumulative risk variable were skewed to the right, with 58% of the participants having no risk factors and 42% having one or more risk factors. Although the regression residuals did not show any skewing, we checked the consistency of our findings by conducting all regression analyses with the cumulative risk variable dichotomized at 0 versus 1 or more risk factors. The results of these analyses did not change the pattern of findings (data not shown). We also tested whether the main and interactive effects were moderated by sex. Because this was not the case, we do not report these findings. All analyses were conducted using the Statistical Package for Social Sciences (SPSS for Windows, version 21.0, SPSS Inc., Chicago).

Results

Descriptive analyses

Descriptive statistics for lnRSA and PEP baseline, challenge episodes and recovery are presented in Supplementary Table 1. lnRSA and PEP response and recovery levels on the SFP and CS were significantly different from zero ($t(105)=4.33, p<.001$ for lnRSA SFP response, $t(97)=3.68, p<.001$ for lnRSA CS recovery, $t(91)=2.56, p<.05$ for PEP SFP response, $t(87)=2.87, p<.01$ for PEP CS response, and $t(82)=-2.28, p<.05$ for PEP CS recovery), except for lnRSA CS response ($t(98)=.23, p=.816$), lnRSA SFP recovery ($t(105)=-1.15, p=.140$), and PEP SFP recovery ($t(87)=.14, p=.889$).

Averaged across the SFP and CS challenge episodes, 63% of the sample showed a decrease in lnRSA (i.e., PNS suppression) and 62% exhibited a decrease in PEP (i.e., SNS activation) from baseline. Averaged across the SFP and CS recovery episodes, 44.5% of the sample showed an increase in lnRSA (i.e., PNS activation) and 54.4% showed an increase in PEP (i.e., SNS suppression) from the challenge episode. Thus, there was sufficient variability in infant lnRSA and PEP response to and recovery from challenge.

Preliminary analyses

Means, SDs, and correlations for the potential covariates and main study variables are presented in Table 1. For interpretation purposes, lnRSA and PEP raw change scores are used for means and SDs in Table 1; however, as noted, residualized change scores are used in the correlation and regression analyses. The demographic characteristics (ethnicity, sex) and obstetric characteristics (gestational age, birth weight) were not significantly related to the main study variables ($ps>.05$). Higher levels of cumulative risk were associated with higher

physical aggression scores ($r=.31, p<.01$). Cumulative risk was not related to response and recovery measures of lnRSA and PEP.

Table 1.

Means, standard deviations and correlations among study variables .

Variable	1.	2.	3.	4.	5.	7.	8.	9.	10.	<i>M</i>	<i>SD</i>	<i>range</i>
1. Cumulative risk	-									.67	.93	0-3
2. Ethnicity (% Caucasian)	.10	-								88.5%		
3. Infant sex (% male)	.08	.07	-							55.8%		
4. Gestational age (weeks)	-.03	-.07	.02	-						39.21	1.85	32-42
5. Birth weight (kg)	-.18†	-.05	-.17†	.62***	-					3.4	.53	1.9-4.5
7. LnRSA response	.02	.15	-.08	-.01	.09	-				.09	.35	-.61-1.14
8. PEP response	-.10	-.08	.18†	-.06	-.10	-.09	-			1.27	3.28	-5.81-11.25
9. LnRSA recovery	-.09	.08	.09	-.16†	-.14	-.15	-.03	-		.02	.26	-.60-.89
10. PEP recovery	-.10	.16	.01	.16	.16	.20*	-.30**	.12	-	-.60	3.69	-14.99-9.67
11. Physical aggression	.28**	.06	-.17†	-.02	-.01	.02	-.18†	.04	-.02	2.85	2.28	0-10

Note: lnRSA = natural logarithm of respiratory sinus arrhythmia, PEP = pre-ejection period. Spearman correlations were used to compute correlations with cumulative risk and Pearson correlations were used for correlations between all other variables. † $p < .10$, * $p < .05$, ** $p < .01$, $p < .001$.

Hierarchical regression analyses

LnRSA and PEP response. Results of the hierarchical regression analysis for LnRSA and PEP response are shown in Table 2. There was a significant main effect of cumulative risk ($b = .65$, $SE = .27$, $p < .05$). Higher cumulative risk predicted higher levels of physical aggression. There were no significant main effects for LnRSA response or PEP response. There were no significant two-way interaction effects between cumulative risk, LnRSA and PEP on physical aggression. However, a significant three-way interaction between cumulative risk x LnRSA response x PEP response was found ($b = -1.23$, $SE = .53$, $p < .05$), explaining 4.7% of the variance in physical aggression over and above the variance explained by cumulative risk, LnRSA and PEP response and all two-way interactions.

Examination of simple slopes (see Figure 1) revealed that for infants exhibiting coactivation (i.e., LnRSA response at 1 *SD* above the mean and PEP response at 1 *SD* below the mean) in response to challenge, higher cumulative risk predicted higher levels of physical aggression ($\beta = .74$, $p < .001$). Conversely, for infants exhibiting coinhibition, reciprocal PNS activation and reciprocal SNS activation in response to challenge, cumulative risk was unrelated to physical aggression ($\beta = .34$, $p = .199$, $\beta = -.05$, $p = .836$, and $\beta = -.02$, $p = .929$ for respectively coinhibition, reciprocal PNS activation and reciprocal SNS activation).

LnRSA and PEP recovery. Results of the hierarchical regression analysis for LnRSA and PEP recovery are shown in Table 2. The main effect for cumulative risk was the same as in the hierarchical regression analysis for LnRSA and PEP response. There were no significant main effects for LnRSA recovery or PEP recovery, and none of two-way or three-way interactions were significant.

Table 2.

Hierarchical regression analyses predicting physical aggression from lnRSA and PEP response and recovery and cumulative risk.

Step	Predictor	<i>LnRSA and PEP response</i>					<i>LnRSA and PEP recovery</i>				
		<i>Adjusted R²</i>	<i>ΔR²</i>	<i>ΔF</i>	<i>β</i>	<i>t</i>	<i>Adjusted R²</i>	<i>ΔR²</i>	<i>ΔF</i>	<i>β</i>	<i>t</i>
1	Cumulative risk	.096	.105	11.51**	.32	3.39**	.089	.089	10.81**	.31	3.29**
2	Cumulative risk	.094	.016	.90	.30	3.11**	.076	.006	.31	.32	3.33**
	lnRSA				.04	.39				.08	.79
	PEP				-.12	-1.25				.02	.18
3	Cumulative risk	.096	.029	1.07	.25	2.38*	.058	.010	.37	.35	3.45**
	lnRSA				.07	.74				.09	.89
	PEP				-.14	-1.40				.04	.39
	lnRSA x PEP				.02	.21				.05	.45
	Cumulative risk x lnRSA				.17	1.66				.09	.84
	Cumulative risk x PEP				-.08	-.76				-.02	-.22
4	Cumulative risk	.137	.047	5.39*	.25	2.46*	.055	.007	.75	.37	3.56**
	lnRSA				.03	.27				.09	.84

PEP	-.12	-1.21	.05	.50
lnRSA x PEP	-.04	-.37	.07	.64
Cumulative risk x lnRSA	.09	.82	.07	.62
Cumulative risk x PEP	-.10	-.97	.01	.10
Cumulative risk x lnRSA x PEP	-.24	-2.32*	.10	.87

Note: * $p < .05$, ** $p < .01$.

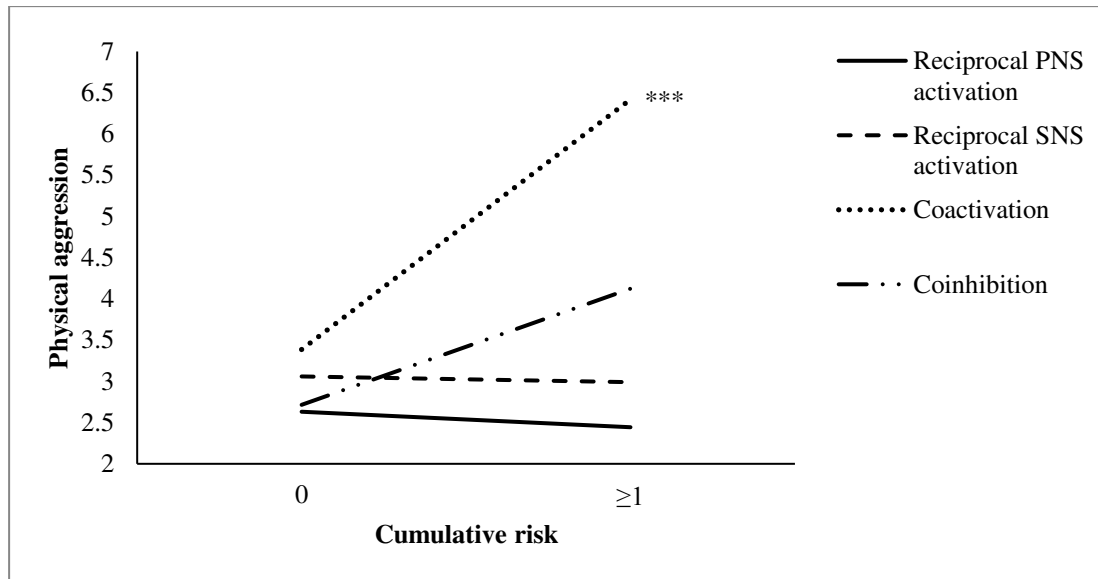


Fig.1. Three-way interaction between lnRSA response, PEP response and cumulative prenatal risk, predicting mother reported physical aggression. lnRSA response and PEP response are plotted 1 *SD* above and 1 *SD* below the mean. Cumulative risk is plotted at 0 risk factors and 1.6 risk factors (this is the average number of risk factors present in infants with one or more risk factors). *Reciprocal PNS activation* refers to PNS activation and SNS inhibition (i.e., lnRSA and PEP response at 1 *SD* above the mean), *reciprocal SNS activation* refers to PNS inhibition and SNS activation (i.e., lnRSA and PEP response at 1 *SD* below the mean), *coactivation* refers to PNS and SNS activation (i.e., lnRSA response at 1 *SD* above the mean and PEP response at 1 *SD* below the mean), and *coinhibition* refers to PNS and SNS inhibition (i.e., lnRSA at 1 *SD* below the mean and PEP response at 1 *SD* above the mean).

*** $p < .001$.

Discussion

Our findings showed that higher levels of coactivation of the PNS and SNS, as reflected in RSA increases and PEP decreases in response to stress, at 6 months increase vulnerability for physical aggression at 20 months, but only in the presence of higher levels of cumulative prenatal risk. Cumulative risk was not associated with physical aggression for infants who exhibited reciprocal PNS activation, reciprocal SNS activation or coinhibition in response to stress. We found no effects for PNS and SNS recovery from stress.

In previous studies, coactivation has been found to operate as a vulnerability factor for aggressive behavior and externalizing behavior problems in school-aged children exposed to adversity (e.g. marital conflict and maltreatment; El-Sheikh et al., 2009; Gordis et al., 2010). Our results extend these findings and indicate that coactivation of the PNS and SNS as represented by RSA and PEP at six months of age predicts physical aggression more than a year later. In fact, physical aggression scores for children exposed to a higher level of prenatal risk and exhibiting coactivation, were more than one standard deviation above the mean physical aggression scores reported in a community sample of 24-month old children (Alink et al., 2006).

Coactivation of the PNS and SNS indicates that both branches of the ANS are activated, and this may yield an ambivalent physiological response in which one branch increases arousal whereas the other branch dampens it (Berntson et al., 1991). Salomon et al. (2000) found that children exhibiting coactivation produced smaller changes in HR in response to challenge than children exhibiting reciprocal SNS activation. Although both coactivators and reciprocal SNS responders activated the SNS, PNS activation buffered the HR response of coactivators, such that these children had the lowest HR reactivity. In situations without challenge or stress, coactivation of the PNS and SNS may operate to preserve the baseline functional state of an organ or system (Berntson et al., 1991). The

results of our study suggest that coactivation, as reflected in RSA increases and PEP decreases in response to challenge reflects a maladaptive ANS response and is linked to poorer developmental outcome. These results support previous findings that PNS activation (i.e., RSA increase) in response to stress is associated with impaired emotion regulation (e.g. Suurland et al., 2016). In case of increases in RSA accompanied by decreases in PEP in response to stress, the PNS continues to exert its inhibitory influence on the SNS and stimulates the body into a calm state, thereby prohibiting an active stress response. Interpreted within the framework of biological susceptibility to context (Boyce & Ellis, 2005), this pattern of stress responsivity may reflect infants' conditional adaptation to a stressful prenatal and early postnatal environment. Moreover, in adverse early postnatal environments patterns of coactivation may lead to consolidation of less adaptive emotion regulation strategies contributing to higher levels of aggression, even more so because in these environments it may be more adaptive for children to act aggressively (i.e., to get what they want, or to get attention from others).

The current study did not provide empirical support for previous findings indicating that coinhibition of the PNS and SNS, as reflected by RSA decreases and PEP increases, also acts as a vulnerability factor for externalizing behavior problems (El-Sheikh et al., 2009; Gordis et al., 2010). It should be noted that these results were obtained in older children exposed to adversity compared to the infants/toddlers in our study. It is possible that coinhibition acts as a biomarker for aggression only later in development, for example after more prolonged exposure to adverse, threatening or stressful situations.

Contrary to our expectations, RSA and PEP recovery did not moderate the impact of prenatal adversity on physical aggression. It is possible that for the majority of infants the recovery period was not long enough to recover from the emotional challenge/stress. Consequently, variance in the RSA and PEP recovery variables was insufficient to reveal

effects on physical aggression. The SFP showed no RSA and PEP recovery, whilst the CS showed a decrease in RSA and an increase in PEP upon recovery, indicating SNS recovery but no PNS recovery on the CS. Few studies to date have addressed ANS recovery from stress (see El-Sheikh & Erath, 2011). One study in adolescents linked blunted SNS recovery to more antisocial behavior (Sijtsema, Van Roon, Groot, & Riese, 2015). Another study in 4-7 year-old children showed that lower vagal recovery was associated with maladaptive emotion regulation strategies to frustration (Santucci et al., 2008). To our knowledge, no other previous studies have examined the association between ANS recovery and outcome in young children, underlining the importance of studying ANS recovery measures in future research.

Recent literature has suggested that measures of heart rate variability (HRV), including RSA, should be considered together with, or adjusted for, HR because of significant overlap between measures of HRV and HR (e.g. Monfredi et al., 2014). There is no consensus as yet on whether HR corrections should be applied or not. Some researchers have noted that correcting HRV measures for HR may be especially important in study populations of young children with a large age range in which growth is likely to have a substantial impact on structural and morphological changes of the heart (Hertzig et al., 2017). We investigated the relation between HR and RSA in our study in additional analyses reported in the Supplementary materials. In line with Hertzig et al. (2017), we found a strong and significant linear correlation between HR and RSA in response to and during recovery from stress. However, adjusting for HR in the regression models did not affect our results, which is consistent with the restricted age range of our study population. In addition, physical aggression could not be predicted from the interaction between cumulative risk and HR alone, suggesting that it is important to examine specific indicators of PNS and SNS activity and

their interaction with cumulative risk in order to gain more insight into which children are more at risk of developing physical aggression.

The findings of this study provide insight into the mechanisms by which prenatal adversity interacts with biological susceptibilities to explain early aggression. However, it is unknown to which extent early adversity has already exerted its influence on the ANS earlier in development, in utero and the first six months of life, and thus influenced this early biological susceptibility for aggression. In the present study, cumulative risk was not related to RSA and PEP activity. However, as noted by Boyce (Boyce, 2016), biology x environment interactions are probably ‘both the originating source and the functional mechanism’ of biological susceptibility to early environments. Future studies should therefore consider both mediating and moderating processes in the study of early adversity, biology and developmental outcomes.

Although this study has some important strengths, including the longitudinal design, the use of specific measures of both PNS and SNS activity, and two different stress tasks, there are also limitations that should be discussed. First, the range of cumulative risk was somewhat restricted, with 42% having one or more risk factors, but only 6% having three risk factors, which may limit the generalizability of our results to samples with higher levels of risk. Another limitation is the reliance on maternal reports of physical aggression. Although the PASEC has shown sufficient validity and reliability in earlier studies, future studies should use multiple informants and methods including behavioral observations of early physical aggression.

The first signs of aggression can already be observed in the first year of life (Hay et al., 2011). Although higher rates of aggression are common around age two (Alink et al., 2006), children who show high levels of aggression as toddlers are at risk for severe and persistent aggressiveness over the course of childhood (Côté et al., 2006; NICHD, 2004).

Understanding the biological mechanisms underlying the earliest forms of aggression is of critical importance, particularly because the ANS still undergoes strong development in the first years of life, which may also render it more malleable and a good target for intervention programs (Beauchaine et al., 2008). Our findings underline the importance of studying patterns of stress reactivity across systems, specifically their interplay, in interaction with adversity during the prenatal period. The results of this study show that coactivation of the PNS and SNS in response to stress may be a biological marker that, already by 6 months of age, increases vulnerability for aggression during toddlerhood. Future studies of how patterns of coactivation develop and whether these can be influenced by intervention are necessary.

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